

10jul03 16:12:33 User217743 Session D610.1  
 \$0.00 0.157 DialUnits FileHomeBase  
 \$0.00 Estimated cost FileHomeBase  
 \$0.00 Estimated cost this search  
 \$0.00 Estimated total session cost 0.157 DialUnits  
 File 410:Chronolog(R) 1981-2003/Aug  
 (c) 2003 The Dialog Corporation

# Set Items Description

-----  
 ? set hi \*:set hi \*  
 HIGHLIGHT set on as '\*\*'  
 \*HIGHLIGHT set on as '\*'  
 ? b 155

10jul03 16:12:36 User217743 Session D610.2  
 \$0.00 0.072 DialUnits File410  
 \$0.00 Estimated cost File410  
 \$0.00 Estimated cost this search  
 \$0.00 Estimated total session cost 0.229 DialUnits  
 File 155:MEDLINE(R) 1966-2003/Jul W1  
 (c) format only 2003 The Dialog Corp.  
 \*File 155: Medline has been reloaded and accession  
 numbers have changed. Please see HELP NEWS 155.

# Set Items Description

-----  
 ? s aids  
 S1 97486 AIDS  
 ? s tn timer (tumour())necrosis()factor)  
 41001 TNF  
 82784 TUMOUR  
 133591 NECROSIS  
 577820 FACTOR  
 7485 TUMOUR(W)NECROSIS(W)FACTOR  
 S2 43218 TNF OR  
 (TUMOUR())NECROSIS()FACTOR)  
 ? s kaposi  
 S3 9002 KAPOSI  
 ? s metabolic()wasting  
 167997 METABOLIC  
 5428 WASTING  
 S4 3 METABOLIC()WASTING  
 ? s s4 and s1  
 3 S4  
 97486 S1  
 S5 1 S4 AND S1  
 ? s wasting and s1  
 5428 WASTING  
 97486 S1  
 S6 647 WASTING AND S1  
 ? s (s6 or s3) and s2  
 647 S6  
 9002 S3  
 43218 S2  
 S7 111 (S6 OR S3) AND S2  
 ? s s6 and s2  
 647 S6  
 43218 S2

S8 39 S6 AND S2  
 ? t s8/3,ab/1-10

8/3,AB/1  
 DIALOG(R)File 155:MEDLINE(R)  
 (c) format only 2003 The Dialog Corp. All rts. reserv.

14546748 22150733 PMID: 12161104

Cytokine responses differ by compartment and  
 \*wasting\* status in patients with HIV infection and  
 healthy controls.

Abad Leslie W; Schmitz Heather R; Parker Russell;  
 Roubenoff Ronenn Department of Community Health,  
 Tufts University School of Medicine, Boston, MA 02111,  
 USA.

Cytokine (United States) Jun 7 2002, 18 (5) p286-93,  
 ISSN 1043-4666 Journal Code: 9005353

Contract/Grant No.: DK45734; DK: NIDDK;  
 MO1-RR00054; RR: NCRR; P01 DK46200; DK: NIDDK  
 Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Inflammatory cytokines are implicated in the loss of  
 lean tissue that occurs in patients with inflammatory and  
 infectious diseases, including HIV infection. However, it  
 is not known whether plasma levels or cellular  
 production of cytokines, or their antagonists, are more  
 closely related to lean tissue loss. We studied whether  
 plasma cytokine analysis could substitute for PBMC  
 production assays in studies of nutrition status and  
 disease state, and if cytokine antagonists could offer an  
 alternative in assessing cytokine status. We used a bout  
 of moderately difficult exercise to perturb cytokine  
 production in 12 adults with HIV without \*wasting\*, 10  
 adults with HIV \*wasting\*, and nine healthy controls.  
 Plasma and peripheral blood mononuclear cell (PBMC)  
 production of interleukin-1 beta (IL-1beta), tumor  
 necrosis factor-alpha (\*TNF\*-alpha), interleukin-6 (IL-6),  
 interleukin-1 receptor antagonist (IL-1ra) and soluble  
 \*TNF\* receptor type II (sTNFrII) were measured at  
 baseline and 2, 6, 24 and 168h following exercise. PBMC  
 production of IL-1beta, \*TNF\*-alpha and IL-6 were all  
 higher in the HIV-infected patients without \*wasting\*  
 than in the controls (P<0.05) or the patients with  
 \*AIDS\* \*wasting\* (P<0.05). Plasma concentrations of  
 \*TNF\*-alpha and IL-6 were higher in the HIV wasted  
 patients than in the controls (P<0.05). Both plasma and  
 PBMC levels of sTNFrII were higher in HIV patients,  
 regardless of \*wasting\*, than in controls. These data  
 suggest that the PBMC cytokine compartment is more  
 sensitive to nutritional and metabolic abnormalities  
 than is the plasma compartment. PBMC production of  
 IL-1beta, IL-6 and \*TNF\*-alpha best distinguish between  
 HIV patients with and without \*wasting\*, while plasma  
 concentrations of IL-6 and \*TNF\*-alpha are elevated  
 in \*AIDS\* \*wasting\*, but do not reliably distinguish  
 patients with \*wasting\* from HIV-infected patients

without \*wasting\*.

8/3,AB/2

DIALOG(R)File 155:MEDLINE(R)

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13926389 22150733 PMID: 12161104

Cytokine responses differ by compartment and \*wasting\* status in patients with HIV infection and healthy controls.

Abad Leslie W; Schmitz Heather R; Parker Russell; Roubenoff Ronenn; et al Department of Community Health, Tufts University School of Medicine, Boston, MA 02111, USA.

Cytokine (United States) Jun 7 2002, 18 (5) p286-93, ISSN 1043-4666 Journal Code: 9005353

Contract/Grant No.: DK45734; DK: NIDDK; MO1-RR00054; RR; NCRR; P01 DK46200; DK: NIDDK; + Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: In Process

Inflammatory cytokines are implicated in the loss of lean tissue that occurs in patients with inflammatory and infectious diseases, including HIV infection. However, it is not known whether plasma levels or cellular production of cytokines, or their antagonists, are more closely related to lean tissue loss. We studied whether plasma cytokine analysis could substitute for PBMC production assays in studies of nutrition status and disease state, and if cytokine antagonists could offer an alternative in assessing cytokine status. We used a bout of moderately difficult exercise to perturb cytokine production in 12 adults with HIV without \*wasting\*, 10 adults with HIV \*wasting\*, and nine healthy controls. Plasma and peripheral blood mononuclear cell (PBMC) production of interleukin-1 beta (IL-1beta), tumor necrosis factor-alpha (\*TNF\*-alpha), interleukin-6 (IL-6), interleukin-1 receptor antagonist (IL-1ra) and soluble \*TNF\* receptor type II (sTNFrII) were measured at baseline and 2, 6, 24 and 168h following exercise. PBMC production of IL-1beta, \*TNF\*-alpha and IL-6 were all higher in the HIV-infected patients without \*wasting\* than in the controls ( $P<0.05$ ) or the patients with \*AIDS\* \*wasting\* ( $P<0.05$ ). Plasma concentrations of \*TNF\*-alpha and IL-6 were higher in the HIV wasted patients than in the controls ( $P<0.05$ ). Both plasma and PBMC levels of sTNFrII were higher in HIV patients, regardless of \*wasting\*, than in controls. These data suggest that the PBMC cytokine compartment is more sensitive to nutritional and metabolic abnormalities than is the plasma compartment. PBMC production of IL-1beta, IL-6 and \*TNF\*-alpha best distinguish between HIV patients with and without \*wasting\*, while plasma concentrations of IL-6 and \*TNF\*-alpha are elevated in \*AIDS\* \*wasting\*, but do not reliably distinguish patients with \*wasting\* from HIV-infected patients without \*wasting\*.

8/3,AB/3

DIALOG(R)File 155:MEDLINE(R)

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11912807 99356149 PMID: 10426694

Geriatric cachexia: the role of cytokines.

Yeh S S; Schuster M W

Geriatric Division, Department of Medicine, VA Medical Center Northport, NY, USA.

Yeh.ShingvShing@Northport.VA.gov

American journal of clinical nutrition (UNITED STATES) Aug 1999, 70 (2) p183-97, ISSN 0002-9165 Journal Code: 0376027

Comment in Am J Clin Nutr. 2000 Mar;71(3) 851-3;

Comment in PMID 10702192 Document type: Journal Article; Review; Review, Tutorial Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Weight loss in elderly patients is a common clinical problem. \*Wasting\* and cachexia are associated with severe physiologic, psychologic, and immunologic consequences, regardless of the underlying causes. Cachexia has been associated with infections, decubitus ulcers, and even death. Multivariate analyses of risk and prognostic factors in community-acquired pneumonia in the elderly have found that age by itself is not a significant factor related to prognosis. Among the significant risk factors, only nutritional status is amenable to medical intervention. Cachexia in the elderly may have profound consequences: medical, cognitive, and psychiatric disorders may diminish self-reliance in activities of daily living, thus reducing quality of life and increasing the frequency of secondary procedures, hospitalizations, and the need for skilled care. Cachexia is associated with higher-than-normal concentrations of tumor necrosis factor alpha (\*TNF\*-alpha), interleukin (IL) 1, IL-6, serotonin, and interferon gamma. The role of these proinflammatory cytokines has been established in the cachexia seen in cancer and \*AIDS\* patients. Reduction in the concentrations of these cytokines is associated with weight gain. Drugs that promote appetite stimulation and weight gain, such as progestational agents, cyproheptadines, pentoxifylline, and thalidomide may work by down-regulating these proinflammatory cytokines. An understanding of the relation between cachexia and negative regulatory cytokines may point to effective treatment of geriatric cachexia as well.

8/3,AB/4

DIALOG(R)File 155:MEDLINE(R)

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11804153 99243391 PMID: 10226804

Interleukin-1 alpha (IL-1 alpha) and tumor necrosis factor alpha (\*TNF\* alpha) regulate insulin-like growth factor binding protein-1 (IGFBP-1) levels and mRNA

abundance in vivo and in vitro.

Benbassat C A; Lazarus D D; Cichy S B; Evans T M;  
Moldawer L L; Lowry S F; Unterman T G

Department of Surgery, Cornell University Medical  
College, New York, USA. Hormone and metabolic  
research. Hormon- und Stoffwechselforschung.  
Hormones et metabolisme (GERMANY) Feb-Mar 1999,  
31 (2-3) p209-15, ISSN 0018-5043 Journal Code:  
0177722

Contract/Grant No.: DK41430-06; DK; NIDDK

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

\*TNF\* alpha and IL-1 alpha are thought to contribute to impaired anabolism in a variety of clinical states, including sepsis, cancer cachexia and the \*AIDS\* \*wasting\* syndrome. We asked whether cytokines exert direct effects on hepatic production of IGFBP-1, an important modulator of IGF bioavailability. C57BL/6 mice were treated with 100 micrograms/kg of recombinant IL-1 alpha or \*TNF\* alpha by intraperitoneal injection. Western ligand blotting and immunoprecipitation with specific antisera revealed that serum levels of IGFBP-1 (but not IGFBP-2, -3, -4, -5 or -6) are increased approximately 4 fold 2 h after treatment and then decline. Northern blotting confirms that hepatic IGFBP-1 mRNA abundance also is increased acutely in both IL-1 alpha- and \*TNF\* alpha-treated animals. Similar results obtained in adrenalectomized mice indicate that adrenal activation is not required for this effect. Cell culture studies show that cytokines exert direct effects on the production of IGFBP-1 by HepG2 hepatoma cells, increasing IGFBP-1 levels in conditioned medium and the abundance of IGFBP-1 mRNA approximately 3-fold. In contrast, transient transfection studies with IGFBP-1 promoter/luciferase reporter gene constructs show that IGFBP-1 promoter activity is reduced after 18 hr cytokine treatment. We conclude that IL-1 alpha and \*TNF\* alpha increase circulating levels of IGFBP-1, reflecting direct effects on hepatic IGFBP-1 mRNA abundance. Stimulation of hepatic IGFBP-1 production may contribute to alterations in IGF bioactivity and impaired anabolism in clinical conditions where cytokine production is high. Additional studies are required to identify specific mechanisms mediating effects of cytokines on hepatic production of IGFBP-1.

8/3,AB/5

DIALOG(R)File 155:MEDLINE(R)

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11640621 99074531 PMID: 9854146

Ubiquitin and proteasome gene expression is increased in skeletal muscle of slim \*AIDS\* patients.

Llovera M; Garcia-Martinez C; Agell N; Lopez-Soriano F J; Authier F J; Gherardi R K; Argiles J M

Departament de Bioquímica i Biologia Molecular,  
Facultat de Biologia, Universitat de Barcelona, Barcelona,  
Spain.

International journal of molecular medicine (GREECE)  
Jul 1998, 2 (1) p69-73, ISSN 1107-3756 Journal  
Code: 9810955

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Human biopsies obtained from skeletal muscle of cachectic \*AIDS\* patients clearly showed an increased expression (in relation to that of healthy subjects) of the genes encoding for the ubiquitin-ATP-dependent proteolytic system. Increases of 120% and 42% were observed for the 2.4 and 1.2 kb ubiquitin transcripts, respectively. The expression of the C8 proteasome subunit was also increased by 60% in the cachectic \*AIDS\* patients in relation to the healthy control subjects. It is suggested that the activation of this proteolytic system (possibly via changes in circulating cytokines, such as \*TNF\* ) may be responsible for the skeletal muscle waste that often accompanies \*AIDS\*.

8/3,AB/6

DIALOG(R)File 155:MEDLINE(R)

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11464123 98347591 PMID: 9682669

Plasma leptin in chronic inflammatory bowel disease and HIV: implications for the pathogenesis of anorexia and weight loss.

Ballinger A; Kelly P; Hallyburton E; Besser R; Farthing M  
Digestive Diseases Research Centre, St Bartholomew's,  
London, U.K. Clinical science (London, England - 1979)  
(ENGLAND) May 1998, 94 (5) p479-83, ISSN  
0143-5221 Journal Code: 7905731

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

1. Leptin inhibits food intake and is an important regulator of long-term energy balance. In rodents, plasma concentrations of leptin are increased by administration of interleukin-1 and \*tumour\* \*necrosis\* \*factor\* . Hyperleptinaemia may mediate the anorexia and weight loss which is observed in chronic infections and inflammatory conditions. 2. Plasma leptin and soluble \*tumour\* \*necrosis\* \*factor\* receptor (sTNF-r55) concentrations were measured in patients with inflammatory bowel disease and acquired immunodeficiency syndrome (\*AIDS\*), and healthy controls. 3. The patients with \*AIDS\* were severely wasted [% body fat 12 (9-16); median (interquartile range)] compared with those with inflammatory bowel disease [25.1 (19-31.5)] and control subjects [29.4 (23.6-37.8)]. Leptin concentrations were highly

correlated with percentage body fat in controls ( $r = 0.74$ ,  $P < 0.001$ ) and patients with IBD ( $r = 0.73$ ,  $P < 0.001$ ) but not in the patients with \*AIDS\* ( $r = -0.024$ ). Leptin concentrations were similar in the inflammatory bowel disease [4.8 (2.6-10.1) ng/ml] and control groups [8.0 (3.1-14.1) ng/ml] but were significantly lower ( $P < 0.05$ ) in patients with \*AIDS\* [1.8 (1.5-2.3) ng/ml] after 23 patients were matched for sex and percentage body fat in patients with inflammatory bowel disease [2.4 (1.8-4.1) ng/ml]. Plasma concentrations of sTNF-r55 were higher in both the patients with inflammatory bowel disease [0.19 (0.16-0.23) ng/ml] and those with \*AIDS\* [4.8 (2.8-7.3) ng/ml] compared with controls [0.14 (0.09-0.16) ng/ml] but were not correlated with either percentage body fat or plasma leptin concentrations. 4. Hyperleptinaemia does not appear to mediate the anorexia and weight loss associated with inflammatory bowel disease and \*AIDS\*. In patients with \*AIDS\* with extreme \*wasting\* there was no relationship between body fat and leptin and this may be related to the rapid weight loss which occurs in these patients.

8/3,AB/7

DIALOG(R)File 155:MEDLINE(R)

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11421201 98303315 PMID: 9641613

Growth hormone, fatigue, poor sleep, and disability in HIV infection. Darko D F; Mitler M M; Miller J C  
Department of Neuropharmacology, Scripps Research Institute, La Jolla, Calif 92037-1027, USA.  
ddarko@scripps.edu

Neuroendocrinology (SWITZERLAND) May 1998, 67 (5) p317-24, ISSN 0028-3835 Journal Code: 0035665  
Contract/Grant No.: 1 P50 MH 47680; MH; NIMH; MO1 RR00833; RR; NCRR Document type: Clinical Trial; Controlled Clinical Trial; Journal Article Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Poor sleep, daytime fatigue, and loss of cognitive ability exist during all stages of HIV infection, worsening with disease progression. These symptoms contribute to disability and poor quality of life. Data from several research groups support a role of somnogenic inflammatory process peptides elevated in HIV infection, e.g. \*TNF\* alpha. Though the literature is in conflict regarding an effect of HIV infection on growth hormone (GH) secretion, GH axis dysregulation and treatment with GH may be important in HIV infection, e.g. in the \*wasting\* syndrome. It has long been known that GH varies with changes in sleep. The hypothesis tested in the current study was that the relationship between delta frequency (0.5-4.0 Hz) sleep EEG amplitude (square root of power from frequency analysis) and GH secretion would differ between HIV

positive (HIV+) and HIV negative (HIV-) subjects. In 14 subjects (6 HIV+ and 8 HIV-, none with current or past \*AIDS\*-defining illness) a linear relationship change across the night's sleep was found in the coupling between delta frequency sleep EEG amplitude and GH secretion. The phase coupling change was in opposite directions in HIV+ versus HIV- subjects. This difference supports the hypothesis that the brain-based coordination of sleep and sleep-related physiology deteriorates early in HIV infection, and that GH dysregulation may contribute to this sleep pathology.

8/3,AB/8

DIALOG(R)File 155:MEDLINE(R)

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11381708 98262759 PMID: 9600025

\*AIDS\* \*wasting\* syndrome as an enterometabolic disorder: the gut hypothesis.

Kaminski M; Weil S; Bland J; Jan P  
FUHS/Chicago Medical School, USA.

Alternative medicine review - a journal of clinical therapeutic (UNITED STATES) Feb 1998, 3 (1) p40-53, ISSN 1089-5159 Journal Code: 9705340

Document type: Journal Article; Review; Review, Tutorial Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

There is an interesting relationship between the HIV virus, the health of the gastrointestinal tract, and \*AIDS\* \*wasting\* syndrome, involving Tumor Necrosis Factor alpha (\*TNF\* alpha), specific and non-specific immunity in the gut, gut permeability, and oxidative stress. It is hypothesized that the progression of HIV to full-blown \*AIDS\* may be impacted by maintaining a healthy gut. A therapeutic protocol which decreases oxidative stress, inhibits \*TNF\* alpha, enhances phase I and II liver detoxification, and improves specific and non-specific immunity in the gut should be part of a therapeutic protocol for HIV-infected individuals. Through a better understanding of the pathophysiology of HIV advancing to \*AIDS\*, the practitioner can develop a treatment strategy of nutritional and lifestyle changes which could theoretically prevent an HIV infection from advancing to full-blown \*AIDS\*.

8/3,AB/9

DIALOG(R)File 155:MEDLINE(R)

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11339443 98219441 PMID: 9558730

Modulation of pro-inflammatory cytokine biology by unsaturated fatty acids.

Grimble R F; Tappia P S

Department of Human Nutrition, University of Southampton, United Kingdom.

Zeitschrift für Ernährungswissenschaft (GERMANY)  
1998, 37 Suppl 1 p57-65, ISSN 0044-264X Journal  
Code: 0413632

Document type: Journal Article; Review; Review, Tutorial  
Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

The production of pro-inflammatory cytokines, such as interleukins 1 and 6 and tumour necrosis factors, occurs rapidly following trauma or invasion of the body by pathogenic organisms. The cytokines mediate the wide range of symptoms associated with trauma and infection, such as fever, anorexia, tissue \*wasting\*, acute phase protein production and immunomodulation. In part, the symptoms result from a co-ordinated response, in which the immune system is activated and nutrients released, from endogenous sources, to provide substrate for the immune system. Although the cytokine mediated response is an essential part of the response to trauma and infection, excessive production of pro-inflammatory cytokines, or production of cytokines in the wrong biological context, are associated with mortality and pathology in a wide range of diseases, such as malaria, sepsis, rheumatoid arthritis, inflammatory bowel disease, cancer and \*AIDS\*. Cytokine biology can be modulated by anti-inflammatory drugs, recombinant cytokine receptor antagonists and nutrients. Among the nutrients, fats have a large potential for modulating cytokine biology. A number of trials have demonstrated the anti-inflammatory effects of fish oils, which are rich in n-3 polyunsaturated fatty acids, in rheumatoid arthritis, inflammatory bowel disease, psoriasis and asthma. Animal studies, conducted by ourselves and others, indicate that a range of fats can modulate pro-inflammatory cytokine production and actions. In summary fats rich in n-6 polyunsaturated fatty acids enhance IL1 production and tissue responsiveness to cytokines, fats rich in n-3 polyunsaturated fatty acids have the opposite effect, monounsaturated fatty acids decrease tissue responsiveness to cytokines and IL6 production is enhanced by total unsaturated fatty acid intake. There are a large number of potential cellular mechanisms which may mediate the effects observed. The majority relate to the ability of fats to alter the composition of membrane phospholipids. As a consequence of alterations in phospholipid composition, membrane fluidity may change, altering binding of cytokines to receptors and G protein activity. The nature of substrate for various signalling pathways associated with cytokine production and actions may also be changed. Consequently, alterations in eicosanoid production and activation of protein kinase C may occur. We have examined a number of these potential mechanisms in peritoneal macrophages of rats fed fats with a wide range of fatty acid composition. We have found that the total C18:2 and 20:4 diacyl species of phosphatidylethanolamine in peritoneal macrophages

relates in a positive curvilinear fashion with dietary linoleic acid intake; that \*TNF\* induced IL1 and IL6 production relate in a positive curvilinear fashion to linoleic acid intake; that leukotriene B4 production relates positively with dietary linoleic acid intake over a range of moderate intakes and is suppressed at high intakes, while PGE2 production is enhanced. There was no clear relationship between linoleic acid intake and membrane fluidity, however fluidity was influenced in a complex manner by the type of fat in the diet, the period over which the fat was fed and the presence of absence of \*TNF\* stimulation. None of the proposed mechanisms, acting alone, can explain the positive effect of dietary linoleic acid intake on pro-inflammatory cytokine production. However each may be involved, in part, in the modulatory effects observed.

8/3,AB/10

DIALOG(R)File 155:MEDLINE(R)

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11246221 98123767 PMID: 9462215 Record  
Identifier: 137343; 00281523 Enteropathy in Zambians  
with HIV related diarrhoea: regression modelling of  
potential determinants of mucosal damage.

Kelly P; Davies S E; Mandanda B; Veitch A; McPhail G;  
Zulu I; Drobniowski F; Fuchs D; Summerbell C; Luo N P;  
Pobee J O; Farthing M J Digestive Diseases Research  
Centre, St Bartholomew's School of Medicine and  
Dentistry, London, UK.

Gut (ENGLAND) Dec 1997, 41 (6) p811-6, ISSN  
0017-5749 Journal Code: 2985108R

TJ: GUT.

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Other Citation Owner: PIP; POP

Abstract Source: PIP

Record type: Completed

BACKGROUND: \*AIDS\* is characterised by small intestinal mucosal damage, but its aetiopathogenesis is poorly understood. Enteric infections in Africa differ from those in northern countries, where protozoan infections have been associated with severe enteropathy in \*AIDS\* patients. AIMS: To characterise enteropathy in Zambian \*AIDS\* patients compared with local controls, and to assess relative contributions of enteric infection, nutritional impairment, and immune dysfunction. METHODS: Computer aided mucosal morphometry of small intestinal biopsy specimens from 56 HIV infected Zambians with persistent diarrhoea and 26 diarrhoea free controls, followed by regression modelling. RESULTS: Patients with HIV related diarrhoea had reduced villous height and increased crypt depth compared with controls. There was no difference between HIV positive and negative controls. In regression models applied to \*AIDS\* mucosal measurements, villous height and crypt depth were

related to nutritional parameters and to serum soluble \*tumour\* \*necrosis\* \*factor\* receptor p55 concentration. Crypt depth was also related to lamina propria plasma cell count. Intestinal infection was found in 79%, which consisted predominantly of microsporidia in 34%, Isospora belli in 24%, and Cryptosporidium parvum in 21%, but detection of these enteropathogens was not related to severity of enteropathy.

CONCLUSIONS: Nutritional and immune disturbances were associated with enteropathy, accounting for over one third of the variation in mucosal morphometric parameters. The relative contributions of enteric infection, nutritional impairment, and immune dysfunction to \*AIDS\*-related enteropathy were investigated in a comparative study of small intestinal biopsy specimens from 56 HIV-positive patients from Lusaka, Zambia, with persistent diarrhea and 26 diarrhea-free controls. Compared with both HIV-positive and HIV-negative controls, patients with HIV-related diarrhea had a 40% reduction in mean villous height and a 19% increase in mean crypt depth. In regression models applied to \*AIDS\* mucosal measurements, villous height and crypt depth were related to nutritional parameters and to the serum soluble tumor necrosis factor receptor p55 concentration. Crypt depth also was related to lamina propria plasma cell count. Intestinal infection, primarily microsporidia, was detected in 79% of cases; however, the presence of enteropathogens was not related to the severity of enteropathy. These findings suggest that nutritional and immune disturbances account for more than 33% of the variation in mucosal morphometric parameters in \*AIDS\*-related enteropathy.

? ds

Set	Items	Description
S1	97486	AIDS
S2	43218	TNF OR (TUMOUR())NECROSIS()FACTOR)
S3	9002	KAPOSI
S4	3	METABOLIC()WASTING
S5	1	S4 AND S1
S6	647	WASTING AND S1
S7	111	(S6 OR S3) AND S2
S8	39	S6 AND S2
? s s8 and py<1997		
	39	S8
	9250212	PY<1997
S9	20	S8 AND PY<1997
? t s9/3,ab/1-10		

9/3,AB/1  
 DIALOG(R)File 155:MEDLINE(R)  
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11125687 97702131 PMID: 11363968  
 Weight loss update.  
 PI perspective (UNITED STATES) Nov \*1996\*, (No 20) p18-9, ISSN 1058-7454 Journal Code: 9102818

Document type: Newspaper Article

Languages: ENGLISH

Main Citation Owner: NLM

Abstract Source: AIDS

Record type: Completed

Unwanted weight loss in people with HIV can be caused by one or more factors simultaneously. A two-pronged approach that addresses the factors causing weight loss and malnutrition, and maintaining or gaining weight is critical. Many opportunistic infections (OIs) can cause diarrhea, but both the drugs used to treat diarrhea and the infections themselves can contribute to weight loss. Lactose intolerance is a common cause of diarrhea in people living with HIV. Because some of the drugs used to treat HIV and OIs are packaged with lactose, it may be necessary to replace the enzymes needed to break down lactose. Appetite loss may also contribute to \*wasting\*, and the lack of nutrients from a lost appetite can tax the body and further aggravate the problem. Appetite stimulants, vitamin supplements, or weight gain products that promote the building of protein are possible treatment options. Lean body mass production may require the use of anabolic (protein building) steroids or testosterone replacement therapy. Another \*wasting\* intervention option involves recombinant human growth hormone (rHGH), however, unsubstantiated safety concerns have arisen on the use of rHGH, and may require increased monitoring. Finally, counteracting weight loss may require adjusting the elevated levels of an immune system chemical called tumor necrosis factor (\*TNF\*) with thalidomide. Because of thalidomide's association with birth defects, sexually active heterosexual women should be advised to use multiple contraceptive mechanisms.

9/3,AB/2  
 DIALOG(R)File 155:MEDLINE(R)  
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10782290 97132507 PMID: 8977962  
 Systemic immune activation as a potential determinant of \*wasting\* in Zambians with HIV-related diarrhoea.  
 Kelly P; Summerbell C; Ngwenya B; Mandanda B; Hosp M; Fuchs D; Wachter H; Luo N P; Pobee J O; Farthing M J  
 University of Zambia School of Medicine Lusaka, Zambia.  
 QJM - monthly journal of the Association of Physicians (ENGLAND) Nov \*1996\*, 89 (11) p831-7, ISSN 1460-2725 Journal Code: 9438285 Document type: Journal Article  
 Languages: ENGLISH  
 Main Citation Owner: NLM  
 Record type: Completed  
 \*Wasting\* in African \*AIDS\* patients is severe, and its aetiology is probably multifactorial: persistent diarrhoea, poverty and tuberculosis may all contribute. We report a cross-sectional study of body composition measured anthropometrically in 75 adult patients with

HIV-related persistent diarrhoea in Lusaka, and its relationship to gastrointestinal infection and systemic immune activation assessed using serum neopterin and soluble \*tumour\* \*necrosis\* \*factor\* receptor (sTNF-R55) concentrations. Patients as a group were generally severely wasted (mean body mass index (BMI) 15.8 kg/m<sup>2</sup>, range 11-22), but the severity of \*wasting\* was related neither to oesophageal candidiasis nor to intestinal infection. In men but not women, all measures of nutritional status were negatively related to serum sTNF-R55 concentration (fat-free mass in men,  $r = -0.64$ ; 95% CI: -0.80, -0.41;  $p < 0.0001$ ). Some wasted patients had cutaneous features of malnutrition, again associated with higher sTNF55 concentrations, and two had peripheral oedema. The diarrhoea- \*wasting\* syndrome in this part of Africa seems to be associated with evidence of high cytokine activity in men, rather than oesophageal candidiasis or any particular intestinal opportunistic infection. This immune activation requires further investigation in the context of the sex difference we have observed.

9/3,AB/3

DIALOG(R)File 155:MEDLINE(R)

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10428013 96234442 PMID: 8699854

Pentoxifylline for the treatment of HIV infection and its complications. Dezube B J; Lederman M M  
Department of Medicine, Beth Israel Hospital,  
Harvard Medical School, Boston, Massachusetts 02215, USA.

Journal of cardiovascular pharmacology (UNITED STATES) \*1995\*, 25 Suppl 2 pS139-42, ISSN 0160-2446 Journal Code: 7902492 Document type: Journal Article; Review; Review, Tutorial Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

The increased levels of tumor necrosis factor-alpha (\*TNF\*-alpha) seen in patients with acquired immune deficiency syndrome (\*AIDS\*) may contribute to the \*AIDS\*-related \*wasting\* syndrome. \*TNF\* also induces expression of human immunodeficiency virus (HIV) through activation of the transcription factor NF-kappa B, which binds to the viral long terminal repeat (LTR). Because \*TNF\* can decrease the antiretroviral activity of zidovudine (AZT) in vitro, pentoxifylline (PTX) may increase the efficacy of AZT. PTX decreases HIV replication in acutely infected cells and inhibits gene expression controlled by the HIV-1 LTR. The antiretroviral activity of PTX is associated with decreased binding of NF-kappa B to its recognition sequences. Therefore, PTX may inhibit HIV expression indirectly by diminishing \*TNF\* production and directly, by decreasing activity of NF-kappa B. PTX, and an inhibitor of the viral transactivator TAT,

Ro24-7429, may inhibit HIV gene expression in a cooperative fashion. The first clinical study of PTX in \*AIDS\* patients was conducted by us through the \*AIDS\* Clinical Trial Group of the National Institutes of Health. \*AIDS\* patients on antiretroviral therapy received PTX 400 or 800 mg three times daily for 8 weeks. \*TNF\* assays included \*TNF\* mRNA levels in peripheral blood mononuclear cells (PBMCs) and inducible \*TNF\* protein levels in the supernatant of PBMCs cultured in the presence of 0.1 microgram/ml lipopolysaccharide (LPS). The median change in \*TNF\* mRNA was a 30% decrease. There was a median and significant 40% decrease in the production of inducible \*TNF\* protein. HIV load decreased in 10 patients and increased in four patients, but did not change in the group as a whole. Others have extended our initial observations in HIV-infected patients. In a placebo-controlled trial, \*TNF\* production by unstimulated PBMCs decreased by 52% in the PTX arm and increased by 7.2% in the placebo arm. In a study comparing AZT, PTX, or a combination of the two, viral load after treatment was ninefold above baseline in the AZT or PTX alone arm, compared to only twofold in the combination arm. In a quality of life trial, PTX was associated with improvement in depression, anger, and social and cognitive function: a placebo effect, however, was not ruled out. PTX 400 mg three times daily is safe and well tolerated. PTX decreases PBMC \*TNF\* expression in HIV-infected patients, measured as protein in culture supernatant or as mRNA, and may decrease viral replication. Further studies of HIV-infected persons are needed to ascertain the benefit of PTX as an adjunct either to inhibitors of reverse transcriptase (e.g., AZT) or of transcription (e.g., TAT inhibitor).

9/3,AB/4

DIALOG(R)File 155:MEDLINE(R)

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10397657 96203095 PMID: 8617220

Muscle \*wasting\* and dedifferentiation induced by oxidative stress in a murine model of cachexia is prevented by inhibitors of nitric oxide synthesis and antioxidants.

Buck M; Chojkier M

Department of Medicine, Veterans Affairs Medical Center, San Diego, CA, USA.

EMBO journal (ENGLAND) Apr 15 \*1996\*, 15 (8) p1753-65, ISSN 0261-4189 Journal Code: 8208664

Contract/Grant No.: DK-38652; DK; NIDDK;

DK-46971; DK; NIDDK; GM-41804; GM; NIGMS; +

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Muscle \*wasting\* is a critical feature of patients

afflicted by \*AIDS\* or cancer. In a murine model of muscle \*wasting\*, tumor necrosis factor alpha (\*TNF\* alpha) induces oxidative stress and nitric oxide synthase (NOS) in skeletal muscle, leading to decreased myosin creatinine phosphokinase (MCK) expression and binding activities. The impaired MCK-E box binding activities resulted from abnormal myogenin-Jun-D complexes, and were normalized by the addition of Jun-D, dithiothreitol or Ref-1, a nuclear redox protein. Treatment of skeletal muscle cells with a phorbol ester, a superoxide-generating system, an NO donor or a Jun-D antisense oligonucleotide decreased Jun-D activity and transcription from the MCK-E box, which were prevented by antioxidants, a scavenger of reducing equivalents, a NOS inhibitor and/or overexpression of Jun-D. The decreased body weight, muscle \*wasting\* and skeletal muscle molecular abnormalities of cachexia were prevented by treatment of \*TNF\* alpha mice with the antioxidants D-alpha-tocopherol of BW755c, or the NOS inhibitor nitro-L-arginine.

9/3,AB/5

DIALOG(R)File 155:MEDLINE(R)

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10378756 96183932 PMID: 8603262

Effects of dietary n-3 fatty acid supplementation in men with weight loss associated with the acquired immune deficiency syndrome: Relation to indices of cytokine production.

Hellerstein M K; Wu K; McGrath M; Faix D; George D; Shackleton C H; Horn W; Hoh R; Neese R A

Department of Nutritional Sciences, University of California, Berkeley, USA.

Journal of acquired immune deficiency syndromes and human retrovirology - official publication of the International Retrovirology Association (UNITED STATES) Mar 1 \*1996\*, 11 (3) p258-70, ISSN 1077-9450 Journal Code: 9501482

Contract/Grant No.: DK-34400; DK: NIDDK;

DK-40995; DK: NIDDK; RR-03300; RR: NCCR

Document type: Clinical Trial; Controlled Clinical Trial;

Journal Article Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Cytokines may be involved in weight loss and disturbances of metabolism associated with human immunodeficiency virus (HIV) infection. Dietary n-3 fatty acids reduce the production of interleukin-1 (IL-1) and tumor necrosis factor (\*TNF\*) by peripheral blood mononuclear cells (PBMC) in normal humans and prevent IL-1 and \*TNF\* anorexia in animals. Accordingly, we studied the nutritional and metabolic effects of a 10-week trial of dietary fish oil (MaxEPA 18 g/day) in men with weight loss due to acquired immune deficiency syndrome (\*AIDS\*). Twenty men were enrolled, and 16 completed the 10-week supplementation period. Prior

weight loss was 13.7 +/- 1.8 kg(17.4 +/- 1.6% body weight, means +/- SE). Food intake, body composition, blood chemistries, serum cytokine concentrations, in vitro production of IL-1 and \*TNF\* by PBMC, and clinical course were followed. A subset of subjects (n=12) underwent stable isotope infusions to measure de novo hepatic lipogenesis (DNL), an in vivo metabolic index that is influenced by cytokine presence and has previously been found to be elevated in \*AIDS\*. An unsupplemented group of men with \*AIDS\* \*wasting\* (10.4 +/- 2.4 kg weight loss, 13.1 +/- 2.2% body weight) was monitored for 10 weeks as controls. Baseline food intake (2,395 +/- 177 kcal/day and 95.1 +/- 7.2 g protein/day), body weight, percent fat, and fat-free mass were unchanged over the 10-week supplementation period. Serum triglycerides were reduced in hypertriglyceridemic subjects, confirming compliance with fish oil supplementation and suggesting that their hypertriglyceridemia was at least in part due to overproduction. Serum \*TNF\* and IL-1 were undetectable before or after fish oil supplementation. Serum interferon alpha (IFN) was measurable but did not change. In vitro production of IL-1 and \*TNF\* by PBMC was markedly reduced both at baseline and after fish oil supplementation in this population, even in the presence of new \*AIDS\* complications, compared with normal controls. The metabolic measurement DNL fell and weight was gained (2.1 +/- 1.3 kg) in subjects who did not develop new \*AIDS\*-related complications, but further increases in DNL and further weight loss were observed in subjects who developed a new \*AIDS\* complication (p<0.05 for interaction between new complication and change in DNL). No changes in body weight, food intake, serum triglycerides, serum cytokines, or DNL were observed in the unsupplemented group. We conclude that fish oil is a weak anticytokine agent that is unable to overcome the metabolic and nutritional consequences of acute \*AIDS\*-related complications but may exert a clinical anticytokine effect in stable \*AIDS\* patients. Cytokine production by PBMC is not a useful or reliable marker of in vivo cytokine activity in \*AIDS\* patients with weight loss. In contrast, an integrative functional index that is sensitive to cytokine presence in tissues (hepatic DNL) correlated with clinical response. These findings are relevant to the design of future studies of more potent anticytokine agents, such as thalidomide.

9/3,AB/6

DIALOG(R)File 155:MEDLINE(R)

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10267411 96069138 PMID: 7577464

Effects of L-carnitine on serum triglyceride and cytokine levels in rat models of cachexia and septic shock.

Winter B K; Fiskum G; Gallo L L

Department of Biochemistry and Molecular Biology,

RC607.AZ6  
J68



George Washington University Medical Center,  
Washington, DC 20037, USA.

British journal of cancer (SCOTLAND) Nov \*1995\*, 72  
(5) p1173-9, ISSN 0007-0920 Journal Code: 0370635

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Inappropriate hepatic lipogenesis, hypertriglyceridaemia, decreased fatty acid oxidation and muscle protein \*wasting\* are common in patients with sepsis, cancer or \*AIDS\*. Given carnitine's role in the oxidation of fatty acids (FAs), we anticipated that carnitine might promote FA oxidation, thus ameliorating metabolic disturbances in lipopolysaccharide (LPS)- and methylcholanthrene-induced sarcoma models of \*wasting\* in rats. In the LPS model, rats were injected with LPS (24 mg kg<sup>-1</sup> i.p.), and treated with carnitine (100 mg kg<sup>-1</sup> i.p.) at -16, -8, 0 and 8 h post LPS. Rat health was observed, and plasma inflammatory cytokines and triglycerides (TG) were measured before and 3 h post LPS. In the sarcoma model, rats were implanted subcutaneously with tumour, and treated continuously with carnitine (200 mg kg<sup>-1</sup> day<sup>-1</sup> i.p.) via implanted osmotic pumps. Tumour burden, TG and cytokines were measured weekly for 4 weeks. Carnitine treatment significantly lowered the tumour-induced rise in TG (% rise) in the sarcoma model (700 +/- 204 vs 251 +/- 51, P < 0.03) in control and carnitine groups respectively. Levels of interleukin-1 beta (IL-1 beta), interleukin-6 (IL-6) and \*tumour\* \*necrosis\* \*factor\* -alpha (\*TNF\* -alpha) (pg ml<sup>-1</sup>) were also lowered by carnitine in both LPS (IL-1 beta: 536 +/- 65 vs 378 +/- 44; IL-6: 271 +/- 29 vs 222 +/- 32; \*TNF\* -alpha: 618 +/- 86 vs 367 +/- 54, P < or = 0.02) and sarcoma models (IL-1 beta: 423 +/- 33 vs 221 +/- 60; IL-6: 222 +/- 18 vs 139 +/- 38; \*TNF\* -alpha: 617 +/- 69 vs 280 +/- 77, P < or = 0.05) for control and carnitine groups respectively. We conclude that carnitine has a therapeutic effect on morbidity and lipid metabolism in these disease models, and that these effects could be the result of down-regulation of cytokine production and/or increased clearance of cytokines.

9/3,AB/7

DIALOG(R)File 155:MEDLINE(R)

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08720891 95700453 PMID: 11362415

Other therapies for \*wasting\*.

Smart T

GMHC treatment issues - the Gay Men's Health Crisis newsletter of experimental AIDS therapies (UNITED STATES) May \*1995\*, 9 (5) p7-8, 12, ISSN 1077-1824 Journal Code: 9509489

Document type: Newspaper Article

Languages: ENGLISH

Main Citation Owner: NLM

Abstract Source: AIDS

Record type: Completed

Individuals with \*wasting\* syndrome lose muscle or lean body mass rather than body fat. Several possible alternatives to the approved drugs for \*AIDS\*-related \*wasting\* are discussed. Ketotifen, an antihistamine approved in Europe, is a \*TNF\* inhibitor. Anabolic steroids are testosterone derivatives designed to increase strength and muscle. Although there are anecdotal reports of success with these steroids, their long-term safety and efficacy have yet to be established in placebo-controlled studies. An ongoing study at Mt. Sinai shows a statistically significant effect on lean body mass in the first twelve men to complete the study. Dehydroepiandrosterone (DHEA) is a hormone produced by the adrenal gland. Although its role in the body is poorly understood; it may have immunologic effects, and appears to influence metabolism. There have been no studies of DHEA's effect on weight or body composition in people with \*AIDS\*-related \*wasting\*. A study combining ketotifen and oxymetholone, the oral anabolic steroid, was presented at the Ninth International \*AIDS\* Conference. Preliminary data from a study combining ketotifen and oxymetholone showed that 18 out of 22 patients gained an average of 11.4 pounds after treatment of an average of 3.9 weeks. Finally, a trial of smoked marijuana versus the oral drug marinol for \*AIDS\*-related \*wasting\* syndrome may be canceled. The Drug Enforcement Administration (DEA) and the National Institute of Drug Abuse (NIDA) rejected the Community Consortium of San Francisco's proposal to obtain officially sanctioned cannabis.

9/3,AB/8

DIALOG(R)File 155:MEDLINE(R)

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08720890 95700452 PMID: 11362414

Growing interest in thalidomide.

Lowell B

GMHC treatment issues - the Gay Men's Health Crisis newsletter of experimental AIDS therapies (UNITED STATES) May \*1995\*, 9 (5) p4-6, ISSN 1077-1824 Journal Code: 9509489

Document type: Newspaper Article

Languages: ENGLISH

Main Citation Owner: NLM

Abstract Source: AIDS

Record type: Completed

Three clinical trials of thalidomide in people with \*AIDS\* are currently underway in the U.S., evaluating it as a treatment for aphthous ulcers, primary HIV infection, or \*wasting\* syndrome. The drug inhibits tumor necrosis factor alpha (\*TNF\*) production and release. (\*TNF\* may play a role in \*wasting\* syndrome and can activate latent HIV in cells.) Thalidomide may also be

studied for a number of other \*AIDS\* -related indications, such as MAC, Kaposi's sarcoma (KS), and lymphomas. In addition, Celgene (the exclusive licensee of a thalidomide use patent filed by Rockefeller University) is developing new analogs of thalidomide that may be more potent and less toxic, although likely more costly. In addition, the Food and Drug Administration (FDA) has been warning buyers clubs not to sell thalidomide. The buyers clubs are cautiously providing access to the drug, but there are requirements: individuals must have a prescription; individuals must have read and signed a booklet on how to use thalidomide safely; and individuals must agree to return any unused medication. A meeting between the buyers clubs and FDA officials is set for the third week in June to discuss thalidomide.

9/3,AB/9

DIALOG(R)File 155:MEDLINE(R)

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08720889 95700451 PMID: 11362413

Inhibiting \*TNF\* to preserve lean body mass.

Smart T

GMHC treatment issues - the Gay Men's Health Crisis newsletter of experimental AIDS therapies (UNITED STATES) May \*1995\*, 9 (5) p3, ISSN 1077-1824 Journal Code: 9509489

Document type: Newspaper Article

Languages: ENGLISH

Main Citation Owner: NLM

Abstract Source: AIDS

Record type: Completed

Researchers suspect that tumor necrosis factor alpha (\*TNF\*), once thought to be a therapy for Kaposi's sarcoma (KS), plays a role in many \*AIDS\* -related complications--neurological difficulties, bone marrow suppression, the growth of KS lesions, and \*AIDS\*-related \*wasting\*. There are several therapies regarded as \*TNF\* reducers, including thalidomide and pentoxifylline, among others. Although many reduce \*TNF\* in the test tube, there are conflicting reports about whether they achieve this effect in the body. Since \*TNF\* can be undetectable in many tests, it may be important for researchers to evaluate closely the markers of immune and viral activity, rather than just \*TNF\* reduction for these drugs.

9/3,AB/10

DIALOG(R)File 155:MEDLINE(R)

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08720879 95700437 PMID: 11362402

Thalidomide and HIV: several possible uses.

Smith D

AIDS treatment news (UNITED STATES) Apr 21

\*1995\*, (no 221) p1-4, ISSN 1052-4207 Journal Code: 8809835

Document type: Newspaper Article

Languages: ENGLISH

Main Citation Owner: NLM

Abstract Source: AIDS

Record type: Completed

Thalidomide is currently under investigation for its proposed value in treating a number of \*AIDS\*-related conditions. Banned in the 1960s because it was found to cause birth defects, thalidomide has been found to inhibit tumor necrosis factor (\*TNF\*), a cytokine associated with the development of aphthous ulcers, dementia, fevers, fatigue and \*wasting\*, as well as enhanced HIV replication. Development rights to use the drug are owned by Celgene, which calls the drug Synovir. Celgene is currently developing several new \*TNF\* inhibitors which are chemically analogous to thalidomide but which might be safer or more effective. Currently, at least 38 sites around the country are testing thalidomide for HIV-related ulcers, and six trial sites are testing for \*wasting\* syndrome. Thalidomide is in trials for the treatment of primary HIV infection at five sites. However, it is unclear whether thalidomide does more to curb HIV activity beyond inhibiting \*TNF\*. Thalidomide trials have been slow to recruit, therefore buyers clubs are working to make the drug available through their services.

? ds

Set	Items	Description
S1	97486	AIDS
S2	43218	TNF OR (TUMOUR())NECROSIS()FACTOR)
S3	9002	KAPOSI
S4	3	METABOLIC()WASTING
S5	1	S4 AND S1
S6	647	WASTING AND S1
S7	111	(S6 OR S3) AND S2
S8	39	S6 AND S2
S9	20	S8 AND PY<1997
? s s3 and s2		
	9002	S3
	43218	S2
	S10	78 S3 AND S2
? s s10 and py<1997		
	78	S10
	9250212	PY<1997
	S11	38 S10 AND PY<1997
? t s11/3,ab/1-10		

11/3,AB/1

DIALOG(R)File 155:MEDLINE(R)

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10668436 97017506 PMID: 8864129

Elevated \*TNF\* -alpha and inducible nitric oxide production by alveolar macrophages after exposure to a nitrite inhalant. Soderberg L S; Chang L W; Barnett J B

Department of Microbiology and Immunology,  
University of Arkansas for Medical Sciences, Little Rock,  
USA.

Journal of leukocyte biology (UNITED STATES) Oct  
\*1996\*, 60 (4) p459-64, ISSN 0741-5400 Journal  
Code: 8405628

Contract/Grant No.: DA06662; DA; NIDA

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Abuse of nitrite inhalants, widespread among male  
homosexuals, has been identified by epidemiological  
studies as an independent risk factor for AIDS and for  
\*Kaposi\*'s sarcoma. Subchronic exposure of mice to  
inhaled isobutyl nitrite was previously found to impair the  
tumoricidal activity of peritoneal macrophages. Because  
inhalants would be expected to have the greatest  
effects on cells in the lung, alveolar macrophages from  
exposed mice were examined in this study. Mice were  
exposed to 900 ppm isobutyl nitrite in an inhalation  
chamber for 45 min/day for 14 days. Following this  
treatment, the lungs of exposed mice had large  
increases in cellularity, both in the alveolar septa and  
within the alveoli. Bronchoalveolar lavages also contained  
increased numbers of cells. Alveolar macrophages  
collected from treated mice had increased tumoricidal  
activity compared with controls and produced higher  
levels of inducible nitric oxide and tumor necrosis  
factor-alpha (\*TNF\*-alpha). The frequency of alveolar  
cells secreting \*TNF\*-alpha was increased ninefold in  
mice exposed to the inhalant. Cell influx into the lung, as  
indicated by the presence of red blood cells in lung  
lavages, was evident after only a single 45-min exposure  
to inhaled isobutyl nitrite at doses as low as 300 ppm.

11/3,AB/2

DIALOG(R)File 155:MEDLINE(R)

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10601722 96419276 PMID: 8822049

[Induction of tumor necrosis factor alpha by  
Mycoplasma penetrans isolated from patients with AIDS]  
Iyama K

Department of Bacteriology in Kurume University School  
of Medicine. Kansenshogaku zasshi. The Journal of  
the Japanese Association for Infectious Diseases  
(JAPAN) Jan \*1996\*, 70 (1) p11-8, ISSN  
0387-5911 Journal Code: 0236671

Document type: Journal Article ; English Abstract

Languages: JAPANESE

Main Citation Owner: NLM

Record type: Completed

The activity of induce tumor necrosis factor alpha  
(\*TNF\* alpha) production of several mycoplasmas,  
including AIDS associated mycoplasmas was investigated.  
M. penetrans which was detected and isolated from urine

and tissue of \*Kaposi\*'s sarcoma of patients with  
AIDS markedly exhibited the induction of \*TNF\* alpha  
production of both THP-1 cells and murine peritoneal  
macrophages to compare to other mycoplasmas. Each  
amount of M. penetrans, M. fermentans, M.  
incognitus, Acholeplasma laidlawii, M. orale, M.  
salivarium, M. hominis required for induction of 50%  
cytotoxicity to L cells in the supernatants of mouse  
peritoneal macrophages cultured with those  
microorganisms was 0.65 micrograms/ml, 11.3  
micrograms/ml, 19.6 micrograms/ml, 6.6 micrograms/ml,  
7.7 micrograms/ml, 6.3 micrograms/ml, 5.7  
micrograms/ml respectively. Next, the components of M.  
penetrans were extracted by Bligh-Dyer method, in  
order to investigate chemical component to induce  
\*TNF\* alpha-production. The activity of \*TNF\* alpha  
induction was mainly found in the methanol-phase, but not  
in the chloroform-phase, where lipid and glycolipid of  
the microorganisms were generally thought to be  
accumulated. The binding of the active component to  
concanavalin A-Sepharose was blocked in the presence of  
Methyl alpha-D-mannopyranoside and Methyl  
alpha-D-glucopyranoside. These results suggest that the  
component possess mannoside and glucoside active site.

11/3,AB/3

DIALOG(R)File 155:MEDLINE(R)

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10352900 96155663 PMID: 8567750

Cultured AIDS-related \*Kaposi\*'s sarcoma (AIDS-KS)  
cells demonstrate impaired bioenergetic adaptation to  
oxidant challenge: implication for oxidant stress in  
AIDS-KS pathogenesis.

Mallery S R; Bailer R T; Hohl C M; Ng-Bautista C L;  
Ness G M; Livingston B E; Hout B L; Stephens R E;  
Brierley G P

Department of Dentistry, College of Dentistry, Ohio  
State University, Columbus 43210-1241, USA.

Journal of cellular biochemistry (UNITED STATES)  
Nov \*1995\*, 59 (3) p317-28, ISSN 0730-2312  
Journal Code: 8205768

Contract/Grant No.: RO1 HL48547; HL; NHLBI

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Despite its recognition as the most prevalent HIV  
associated cancer, speculation still abounds regarding  
the pathogenesis of AIDS-related \*Kaposi\*'s sarcoma  
(AIDS-KS). However, it has been established that both  
cytokines, e.g. IL-6, and HIV-associated products, e.g.,  
Tat, are integral in AIDS-KS cellular proliferation.  
Further, both experimental and clinical evidence is  
accumulating to link reactive oxygen intermediates (ROI)  
with both cytokine induction (primarily via nuclear  
factor-kappa B[NF-kappa B] dependent routes) as well  
as the subsequent cytokine, tumor necrosis factor alpha

(\*TNF\* alpha) stimulation of HIV replication. Features of AIDS-KS patients, such as retention of phagocytes, presence of sustained immunostimulation, and a frequent history of KS lesions arising at traumatized sites, make oxidant stress a viable clinical factor in AIDS-KS development. Time course nucleotide profile analyses show that AIDS-KS cells have an inherent, statistically significant, biochemical deficit, even prior to oxidant stress, due to 1) a more glycolytic bioenergetic profile, resulting in lower levels of high energy phosphates (impairing capacity for glutathione [GSH] synthesis and DNA repair); 2) lower levels of NADPH (compromising the activities of GSSG reductase and peroxidase function of catalase); and 3) reduced levels of GSH (impeding both GSH peroxidase and GSH-S-transferases). Following exposure to physiologically relevant levels of H<sub>2</sub>O<sub>2</sub>, only the human microvascular endothelial cells (a putative AIDS-KS progenitor cell) responded with bioenergetic adaptations that reflected co-ordination of energy generating and cytoprotective pathways, e.g., retention of the cellular energy charge, increased NAD<sup>+</sup>, and an accentuation of the ATP, NADPH, and total adenine nucleotide differences relative to AIDS-KS cells. Also, some of the AIDS-KS strains retained intracellular GSSG subsequent to oxidant challenge, inviting the formation of deleterious protein mixed disulfides. While the results of our study address some AIDS-KS issues, they also raise an etiological question, i.e., Does the inability to tolerate oxidant stress arise in conjunction with AIDS-KS neoplastic development, or is it pre-existing in the population at risk? Regardless, use of antioxidant therapy (low risk/ potentially high benefit) in both the "at risk" population as well as in those individuals with active disease may prove a useful preventative and/or treatment modality.

11/3,AB/4  
 DIALOG(R)File 155:MEDLINE(R)  
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10289037 96090904 PMID: 7501912  
 [Thyroid and AIDS]  
 Thyroide et SIDA.  
 Bonnyns M; Bourdoux P  
 Departement de Medecine, Hopital Universitaire  
 Saint-Pierre. Revue medicale de Bruxelles (BELGIUM)  
 Nov \*1995\*, 16 (5) p361-3, ISSN 0035-3639 Journal  
 Code: 8003474  
 Document type: Journal Article; Review; Review,  
 Multicase ; English Abstract  
 Languages: FRENCH  
 Main Citation Owner: NLM  
 Record type: Completed  
 Two types of thyroid biochemical abnormalities  
 (TBA) are observed in AIDS. The unspecific TBA are  
 similar to TBA reported in the Euthyroid Sick Syndrome.

An increased serum TBG of unknown origin and a decreased circulating rT<sub>3</sub> are the most specific TBA of AIDS. The latter abnormality may be in relation with an elevated level of \*TNF\*. The frequency of serum antithyroid antibodies seems higher than in control groups. Opportunistic infections of the thyroid gland or destruction of the thyroid by \*Kaposi\*'s sarcoma are also reported in AIDS.

11/3,AB/5  
 DIALOG(R)File 155:MEDLINE(R)  
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10231241 96032543 PMID: 7556640  
 Transfection of cells with basic fibroblast growth factor and \*Kaposi\* fibroblast growth factor genes induce resistance to and receptor modulation of tumor necrosis factor.  
 Aggarwal B B; Pocsik E; Totpal K  
 Department of Molecular Oncology, University of Texas M.D. Anderson Cancer Center, Houston 77030, USA.  
 FEBS letters (NETHERLANDS) Sep 18 \*1995\*, 372 (1) p44-8, ISSN 0014-5793 Journal Code: 0155157  
 Document type: Journal Article  
 Languages: ENGLISH  
 Main Citation Owner: NLM  
 Record type: Completed  
 Tumor necrosis factor (\*TNF\*) has been shown to inhibit the growth of some cell types and stimulate the proliferation of others by a mechanism that is not understood. In the present study, we investigated the effect of transfection of NIH-3T3 cells with either the basic fibroblast growth factor gene (bFGF) or the \*kaposi\* FGF gene (K-fgf) on the growth-modulatory effects of \*TNF\*. Our results show that transformation of cells with either gene leads to resistance to the growth-inhibitory effects of \*TNF\*. The K-fgf gene was found to be a more potent inducer of cellular resistance than the bFGF gene. The cellular resistance correlated with the inhibition of \*TNF\*-induced activation of phospholipase A<sub>2</sub> and down-modulation of \*TNF\* receptors. Overall, our results indicate that both K-fgf and bFGF play an important role in suppression of antiproliferative effects of \*TNF\*.

11/3,AB/6  
 DIALOG(R)File 155:MEDLINE(R)  
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08720890 95700452 PMID: 11362414  
 Growing interest in thalidomide.  
 Lowell B  
 GMHC treatment issues - the Gay Men's Health  
 Crisis newsletter of experimental AIDS therapies

(UNITED STATES) May \*1995\*, 9 (5) p4-6 , ISSN 1077-1824 Journal Code: 9509489

Document type: Newspaper Article

Languages: ENGLISH

Main Citation Owner: NLM

Abstract Source: AIDS

Record type: Completed

Three clinical trials of thalidomide in people with AIDS are currently underway in the U.S., evaluating it as a treatment for aphthous ulcers, primary HIV infection, or wasting syndrome. The drug inhibits tumor necrosis factor alpha (\*TNF\*) production and release. (\*TNF\* may play a role in wasting syndrome and can activate latent HIV in cells.) Thalidomide may also be studied for a number of other AIDS-related indications, such as MAC, \*Kaposi\*'s sarcoma (KS), and lymphomas. In addition, Celgene (the exclusive licensee of a thalidomide use patent filed by Rockefeller University) is developing new analogs of thalidomide that may be more potent and less toxic, although likely more costly. In addition, the Food and Drug Administration (FDA) has been warning buyers clubs not to sell thalidomide. The buyers clubs are cautiously providing access to the drug, but there are requirements: individuals must have a prescription; individuals must have read and signed a booklet on how to use thalidomide safely; and individuals must agree to return any unused medication. A meeting between the buyers clubs and FDA officials is set for the third week in June to discuss thalidomide.

11/3,AB/7

DIALOG(R)File 155:MEDLINE(R)

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08720889 95700451 PMID: 11362413

Inhibiting \*TNF\* to preserve lean body mass.

Smart T

GMHC treatment issues - the Gay Men's Health Crisis newsletter of experimental AIDS therapies

(UNITED STATES) May \*1995\*, 9 (5) p3, ISSN

1077-1824 Journal Code: 9509489

Document type: Newspaper Article

Languages: ENGLISH

Main Citation Owner: NLM

Abstract Source: AIDS

Record type: Completed

Researchers suspect that tumor necrosis factor alpha (\*TNF\*), once thought to be a therapy for \*Kaposi\*'s sarcoma (KS), plays a role in many AIDS-related complications--neurological difficulties, bone marrow suppression, the growth of KS lesions, and AIDS-related wasting. There are several therapies regarded as \*TNF\* reducers, including thalidomide and pentoxifylline, among others. Although many reduce \*TNF\* in the test tube, there are conflicting reports about whether they achieve this effect in the body. Since \*TNF\* can be

undetectable in many tests, it may be important for researchers to evaluate closely the markers of immune and viral activity, rather than just \*TNF\* reduction for these drugs.

11/3,AB/8

DIALOG(R)File 155:MEDLINE(R)

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08720876 95700427 PMID: 11362396

Tumor necrosis factor: its role in HIV/AIDS.

Drexler A M

Bailey - Boushay House, Seattle, WA.

STEP perspective (UNITED STATES) Spring \*1995\*, 7 (1) p13-5, Journal Code: 9888939

Document type: Newspaper Article

Languages: ENGLISH

Main Citation Owner: NLM

Abstract Source: AIDS

Record type: Completed

Tumor necrosis factor (\*TNF\* , cachectin), a cytokine secreted by macrophages and T-cells, mediates inflammatory and immune responses, and is associated with wasting in persons with malignancies or AIDS. In inflammation, \*TNF\* attracts and activates neutrophils, stimulating phagocytic function of neutrophils and macrophages. \*TNF\* also increases hepatic cell resistance to damaging parasitic effects; enhances endothelial permeability, causing edema; aids in wound healing by stimulating tissue and vascular growth; enhances lymphocytic activity through cytokine activation; acts with interleukin (IL) to produce fever, anorexia, lethargy and sleep; and possesses antitumor activity, particularly against the presumed origin of \*Kaposi\*'s sarcoma, capillary endothelial cells. The host has an acute phase response (APR) following \*TNF\*- and IL-induced immunologic activation. \*TNF\* and IL decrease production and activity of lipoprotein lipase (LPL), resulting in reduced uptake and improper storage of fat; and they stimulate anabolism of fatty acids, causing hypertriglyceridemia. This "futile cycling" causes shuttling of fatty acids between adipose tissue and the liver, and use of muscle protein as the main fuel source. This, along with further muscular breakdown due to the increased caloric demands of fever, may affect cachexia. \*TNF\* benefits the HIV-infected through selective killing of HIV-infected cells, although effects may be dose and time dependent. The negative effects of \*TNF\* may be impeded by anti-cytokine therapy. Possible therapies include dietary N-3 fatty acid (fish oil), an inhibitor of \*TNF\* and IL production *in vitro*; pentoxifylline (Trental), another \*TNF\* production inhibitor; anti-\*TNF\* monoclonal antibodies; and soluble \*TNF\* receptors.

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DIALOG(R)File 155:MEDLINE(R)

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08687913 95376518 PMID: 7648450

Comparison of constitutive cytokine release in high and low histologic grade AIDS-related \*Kaposi\*'s sarcoma cell strains and in sera from HIV+/KS+ and HIV+/KS- patients.

Bailer R T; Lazo A; Ng-Bautista C L; Hout B L; Ness G M; Hegtvold A K; Blakeslee J R; Stephens R E; Brierley G P; Mallory S R

Department of Veterinary Pathobiology, College of Dentistry, Ohio State University, Columbus, USA.

Journal of interferon & cytokine research - the official journal of the International Society for Interferon and Cytokine Research (UNITED STATES) May \*1995\*, 15 (5) p473-83, ISSN 1079-9907 Journal Code: 9507088

Contract/Grant No.: RO1 HL48547; HL; NHLBI

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

\*Kaposi\*'s sarcoma (KS) is both an AIDS-defining disease and the most common HIV-associated malignancy. A cytokine-mediated pathogenesis for AIDS-KS is implicated because AIDS-KS-derived cell strains both respond to and express a variety of cytokines. We have reported the establishment of several (n = 18) AIDS-KS cell strains and determined that reduced exogenous growth factors are necessary to sustain proliferation in isolates from high histologic grade KS lesions. This current investigation explored the possibility that there are histologic grade-associated differences in either the qualitative and/or quantitative constitutive release of AIDS-KS growth stimulatory cytokines. Our findings showed that the incorporation of HTLV-II cytokine-rich conditioned media induced both qualitative and significant quantitative cytokine release, suggesting that exogenous growth promoters stimulate constitutive cytokine release. ELISA of our AIDS-KS cell strains demonstrated constitutive release of IL-6 (seven of seven), FGF-2 (five of seven), GM-CSF (three of seven), and IL-1 beta (one of seven). None of our AIDS-KS cell strains constitutively released detectable levels of Onco-M, IL-4, PDGF, \*TNF\*-alpha, or \*TNF\*-beta. In addition, we report that the method of cytokine result quantitation significantly affects reported cytokine levels. We determined that there was no significant histologic grade-dependent difference in the constitutive release of soluble cytokines by in vitro grown cultures of AIDS-KS cells. The presence of HIV influenced the sera cytokine profiles by elevating IL-6 and decreasing PDGF concentrations of HIV+ individuals relative to HIV- healthy controls. However, the presence of KS was not associated with unique serum cytokine profiles, because no differences were noted in comparisons of HIV+/KS+ versus HIV+/KS- individuals.

Our findings suggest that the local environment is key in modulating AIDS-KS cytokine expression and that KS growth-promoting factors function at the local or paracrine, not the systemic, level. In conclusion, our previous results demonstrated a histologic grade-associated difference in the in vitro growth capacity of AIDS-KS cells; with high histologic grade isolates displaying a marked growth advantage during culture in minimally supplemented media. Findings from this current study reveal that although the potential for a constitutive growth loop exists in the high-grade isolates, it is not reflected in the free levels of soluble cytokines secreted into the culture medium.

11/3,AB/10

DIALOG(R)File 155:MEDLINE(R)

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08674259 95362858 PMID: 7543496

Platelet activating factor produced in vitro by \*Kaposi\*'s sarcoma cells induces and sustains in vivo angiogenesis.

Bussolino F; Arese M; Montrucchio G; Barra L; Primo L; Benelli R; Sanavio F; Aglietta M; Ghigo D; Rola-Pleszczynski M R; et al

Dipartimento di Genetica, Biologia e Chimica Medica, University of Torino, Italy.

Journal of clinical investigation (UNITED STATES) Aug \*1995\*, 96 (2) p940-52, ISSN 0021-9738 Journal Code: 7802877

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Imbalance in the network of soluble mediators may play a pivotal role in the pathogenesis of \*Kaposi\*'s sarcoma (KS). In this study, we demonstrated that KS cells grown in vitro produced and in part released platelet activating factor (PAF), a powerful lipid mediator of inflammation and cell-to-cell communication. IL-1, \*TNF\*, and thrombin enhanced the synthesis of PAF. PAF receptor mRNA and specific, high affinity binding site for PAF were present in KS cells. Nanomolar concentration of PAF stimulated the chemotaxis and chemokinesis of KS cells, endothelial cells, and vascular smooth muscle cells. The migration response to PAF was inhibited by WEB 2170, a hexazepinoic PAF receptor antagonist. Because neoangiogenesis is essential for the growth and progression of KS and since PAF can activate vascular endothelial cells, we examined the potential role of PAF as an instrumental mediator of angiogenesis associated with KS. Conditioned medium (CM) from KS cells (KS-CM) or KS cells themselves induced angiogenesis and macrophage recruitment in a murine model in which Matrigel was injected subcutaneously. These effects were inhibited by treating mice with WEB 2170. Synthetic PAF or natural

*Microfilm*

PAF extracted from plasma of patients with classical KS also induced angiogenesis, which in turn was inhibited by WEB 2170. The action of PAF was amplified by expression of other angiogenic factors and chemokines: these included basic and acidic fibroblast growth factor, placental growth factor, vascular endothelial growth factor and its specific receptor flk-1, hepatocyte growth factor, KC, and macrophage inflammatory protein-2. Treatment with WEB 2170 abolished the expression of the transcripts of these molecules within Matrigel containing KS-CM. These results indicate that PAF may cooperate with other angiogenic molecules and chemokines in inducing vascular development in KS.

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6208 TNF/TI

4443 KAPOSI/TI

S12 1 TNF/TI AND KAPOSI/TI

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DIALOG(R)File 155:MEDLINE(R)

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11755271 99192789 PMID: 10092829

Implication of \*TNF\* receptor-I-mediated extracellular signal-regulated kinases 1 and 2 (ERK1/2) activation in growth of AIDS-associated \*Kaposi\* 's sarcoma cells: a possible role of a novel death domain protein MADD in \*TNF\*-alpha-induced ERK1/2 activation in \*Kaposi\* 's sarcoma cells.

Murakami-Mori K; Mori S; Bonavida B; Nakamura S  
Department of Microbiology and Immunology,  
University of California, School of Medicine, Los Angeles  
90095, USA.

Journal of immunology (Baltimore, Md. - 1950)  
(UNITED STATES) Mar 15 1999, 162 (6) p3672-9,  
ISSN 0022-1767 Journal Code: 2985117R Document  
type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

TNF-alpha is a key pathogenic mediator of infectious and inflammatory diseases. HIV infection stimulates and dysregulates the immune system, leading to abnormal production of TNF-alpha. Despite its cytotoxic effect on some tumor cell lines, TNF-alpha functions as a growth stimulator for Kaposi's sarcoma (KS), a common malignancy in HIV-infected patients. However, signaling pathways linked to TNF-alpha-induced mitogenic responses are not well understood. We found that extracellular signal-regulated kinases 1 and 2 (ERK1/2) in KS cells were significantly activated by TNF-alpha through tyrosine/threonine phosphorylation. Using neutralizing anti-TNFR-I and TNFR-II mAbs, we have now obtained evidence that TNF-alpha-induced KS cell growth and ERK1/2 activation are mediated exclusively by TNFR-I, not by TNFR-II. A selective

inhibitor for ERK1/2 activator kinases, PD98059, profoundly inhibited not only the activation of ERK1/2, but also the TNF-alpha-induced KS cell proliferation. We therefore propose that the TNFR-I-ERK1/2 pathway plays a pivotal role in transmitting to KS cells the mitogenic signals of TNF-alpha. TNFR-I possesses no intrinsic kinase activity, suggesting that TNFR-I-associated proteins may provide a link between TNFR-I and ERK1/2 activation. We found that actinomycin D treatment of KS cells selectively abolished expression of mitogen-activated protein kinase-activating death domain protein (MADD), a novel TNFR-I-associated death domain protein. TNF-alpha failed to induce ERK1/2 activation in the actinomycin D-treated cells. MADD may couple TNFR-I with the ERK1/2 signaling pathway required for KS cell proliferation.

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